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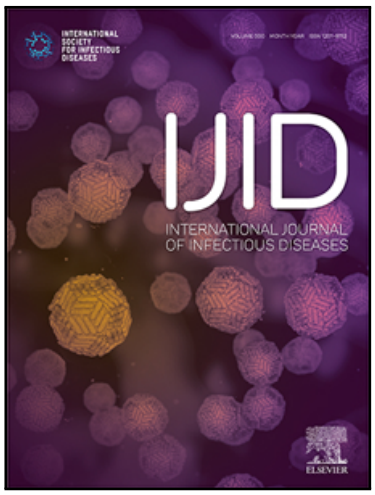


# Follow-up study on the COVID-19 survivors after one year discharged from hospital

Yumiao Zhao , Chunxia Yang , Xiaocai An , Yajun Xiong , Yaomin Shang , Jiarong He , Yan Qiu , Ning Zhang , Lisha Huang , Junli Jia , Qinfu Xu , Long Zhang , Junjie Zhao , Guangzhong Pei , Hong Luo , Jun Wang , Qingquan Li , Yanfeng Gao , Aiguo Xu

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**Highlights:**

- The prevalence of muscle fatigue and insomnia up to 1-year after COVID-19 is high.
- The prevalence of anxiety or depression up to 1-year after COVID-19 is high.
- Survivors with radiological anomalies had older age.
- Survivors with impairment of DLCO had higher urea nitrogen levels.
- The level of SARS-CoV-2 NAb and IgG at 1-year after discharge were decreased.

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# Follow-up study on the COVID-19 survivors after one year discharged from hospital

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**Abstract**

**Objective:** To evaluate the long-term consequences of survivors with COVID-19 one year after recovery, and to identify the risk factors associated with abnormal patterns in chest imaging manifestations, or impaired lung function.

**Methods:** COVID-19 patients were recruited and prospectively followed up with symptoms, HRQoL (health-related quality of life), psychological questionnaires, 6MWT (6-minute walking test), chest CT, PFTs and blood tests. Multivariable logistic regression models were used to evaluate the association between the clinical characteristics and the chest CT abnormalities or the pulmonary function.

**Results:** Ninety-four patients with COVID-19 were recruited between January 16 and February 6, 2021. Muscle fatigue and insomnia were the most common symptoms. Chest CT scan were abnormal in 71.28% of participants. Results of multivariable regression showed an increase odd in age. Ten patients had impairment of DLCO (diffusing capacity of the lung for carbon monoxide). Urea nitrogen concentration on admission was significantly associated with impaired DLCO. The level of IgG and the

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neutralizing activity were significantly lower compared with those at the early phase.

**Conclusions**: One year after hospitalization for COVID-19, a cohort of survivors were mainly troubled with muscle fatigue and insomnia. Pulmonary structural abnormalities and pulmonary diffusion capacities were highly prevalent in surviving COVID-19 patients. It is necessary to intervene main target population for long-term recovery.

**Key words:** COVID-19; CT abnormalities; lung function; Neutralizing antibodies; IgG antibody.

## Introduction

The epidemic of coronavirus disease 2019 (COVID-19), arising from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 190 million confirmed cases with more than 4.0 million deaths (WHO, 2021). Survivors with COVID-19 are frequently reported to have persistent symptoms, pulmonary function and psychological problems. It is challenging and necessary to evaluate the long-term sequelae of COVID-19.

Persistent pulmonary function impairment and health status were demonstrated in survivors of SARS up to 1 year following hospital discharge(Hui et al., 2005; Ong et al., 2005; Ruhl et al., 2017). Higher titers of antibody against SARS, MERS, and H7N9 continued to persist for 1 year(Choe et al., 2017; Ma et al., 2018; Xie et al., 2005). There are several reports of long-term consequences of COVID-19 at 3-month and 6-month post-discharge(Gonzalez et al., 2021; Huang et al., 2021; Qin et al., 2021;

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Tarsitani et al., 2021; Zhao et al., 2020), but the prevalence and severity of the long-term sequelae of COVID-19 remained largely unknown.

Herein, we systematically assess, 1 year after discharge, the long-term health consequences of survivors of COVID-19. Participants in this study underwent an evaluation of health status, involving the 36-Item Short-Form Health Survey (SF-36), the 14-item Hamilton Anxiety Rating Scale (HAMA-14), the 24-item Hamilton Depression Rating Scale (HAMD-24), the modified British Medical Research Council (mMRC) and exercise test (6-minute walking test (6MWT)). The characterization of chest CT, lung function, and titers of antibodies were also examined.

## Materials and Methods

### Study design and participants

This prospective observational study included six cohorts of adult inpatients (≥ 18 years old). All adult patients with laboratory-confirmed SARS-CoV-2 infection, and subsequently admitted centrally to the designated local hospitals in Henan Province, were enrolled. This study has been approved by the Institutional Review Board of the relevant centers. All participants remained anonymous, and written informed consent was obtained. This study was registered with the Chinese Clinical Trial Registry, ChiCTR2000033186. The World Health Organization's (WHO) interim guidance diagnosis for adults with COVID-19 was used (WHO, 2020).

### Data collection

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Baseline and hospital stay

The clinical data of all participants were extracted from electronic medical records, containing sociodemographic, time of admission, length of hospital stay and comorbidity. Clinical classification of COVID-19, blood routine outcomes and therapeutic were also recorded. All data were checked by three physicians.

12-month follow-up

Follow-up consultations were done in the outpatient clinic of the relevant centers. We conducted face-to-face interviews by trained physicians and all participants were asked to complete a series of questionnaires. For the symptom questionnaire, participants were asked to report new symptoms onset after COVID-19. All participants received 6MWT, PFTs, high resolution CT of the chest, and antibody tests.

For general and respiratory symptoms, participants were asked to report persistent symptoms of patients after COVID-19. Items such as fatigue, muscle weakness, joint paint, sleep difficulties, headache, hair loss, chest pain, smell or taste disorder, myalgia, palpitations, dizziness, sore throat or difficult to swallow, diarrhea or nausea and skin rash were assessed. Furthermore, we used the Chinese version of HAMA-14 and HAMD-24 to evaluate signs and symptoms of anxiety and depression(Lu et al., 2020). Overall, participants with HAMA scores of 0-6, 7-13 and ≥ 14 points were categorized as having no, mild/moderate anxiety, and severe anxiety, respectively(Qin et al., 2020). The total score of HAMD is operationally categorized as follows: normal (score 0-6), mild or probable depression (score 7-17), moderate or definite depression

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(score 18-24) and severe depression (score ≥ 25)(Zhuang et al., 2018). The SF-36 is a well-known health-related quality of life (HRQoL) questionnaire that comprehensively measures 8 aspects to access physical and mental health: physical function (PF), role physical (RP), body pain (BP), general health perceptions (GH), vitality (VT), social function (SF), role emotional (RE) and mental health (MH)(Apolone et al., 1998). It presents a score of 0 to 100 with a higher score indicating better health status.

**Chest CT acquisition and image analysis**

Each subject underwent initial chest CT examination and follow-up examinations during a single-breath at full inspiration. All CT scans were acquired with the patients in the supine position with both limbs raised above the head. The whole-lung spiral CT scan was performed from the apex to the base of the lungs. The CT scanner models from the hospitals involved in this multicenter study were listed as following: Somatom Definition AS 128, Philips Brilliance 16, Philips Brilliance 64, Philips Incisive 64. All images were then reconstructed with a slice of 1.0-5.0 mm with the same increment.

Two radiologists who were blinded to the clinical information, independently reviewed and scored the CT images. When there is a divergent opinion, they would make the finial decision via a view console. The radiologists assessed the following eight characteristics(Guler et al., 2021): ground glass opacities (GGO), consolidation, nodule, reticulation, interlobular septal thickening, crazy-paving patter, subpleural

curvilinear line and pulmonary fibrosis. The CT-score is derived from abnormal pulmonary involvement based on a 5 point scale (0: normal; 1: < 5%; 2: 5-25%; 3: 26-50%; 4: 51-75%; 5 > 75%). A total score was eventually recorded via the addition of the score of individual segment.

**Pulmonary Function tests**

Outpatient PFTs were done in the Lung Function Laboratory of the Guangshan People's Hospital and Xixian People's Hospital using MasterScreen PFT (Jaeger, Germany) or MasterScreen (Jaeger, Germany) according to ATS-ERS guidelines(Graham et al., 2019). The PFTs yielded the following parameters: forced expiratory volume in the first second ($FEV_1$), forced vital capacity (FVC), $FEV_1$/FVC, FVC% pred, diffusing capacity of the lung for carbon monoxide (DLCO).

**Dynamic changes of SARS-CoV-2 IgG and IgM antibodies, neutralizing antibodies**

Serum IgM and IgG antibodies against SARS-CoV-2 spike protein (S) and the nucleocapsid protein (N) were measured by the commercial kit provided by YHLO biotechnology (Catalog number, G86095M/G86095G), which been previously described(Zhao et al., 2020). The cut-off for positivity is equal to 10.0 AU/mL for both IgM and IgG according to the manufacturer. The SARS-CoV-2 neutralizing antibodies (NAb) were measured by the SARS-CoV-2 sVNT kit (Catalog number, L00847, GenScript) according to the manufacturer instructions(Tan et al., 2020). The

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inhibition of the sample is proportional to the titer of the anti-SARS-CoV-2 neutralizing antibodies. There were 55 (including 4 mild, 47 moderate, and 4 severe diseases)(Zhao et al., 2020) at 3-month after discharge and 67 survivors (including 2 mild, 30 moderate 33 severe and 2 critical cases) at 1-year after discharge tested for IgM, IgG and NAb against SARS-CoV-2.

**Statistical analysis**

Categorical variables were expressed as number (percentage) and compared using Chi-square test or Fisher exact test. Continuous data were described as mean ± SD (standard deviation), followed by paired or unpaired t-test or Mann-Whitney test or Wilcoxon test. Multivariable logistic regression modes were used to explore the risk factors associated with chest CT abnormalities or impaired DLCO. The correlation of different variables was analyzed using the Spearman's correlation. All analyses were performed using SPSS 21.0 and GraphPad Prism 8.0. Two-sided $P < 0.05$ was considered as statistically significant.

**Results**

A total of 272 patients with COVID-19 were discharged from relevant hospitals and the follow-up study was done from Jan 16, 2021 and Feb 6, 2021. One hundred and eighty survivors did not attend follow-up study for several reasons which were outlined in Figure 1. Finally, 94 adult participants which included 3 cases of mild pneumonia, 48 cases of pneumonia, 41 cases of severe pneumonia and 2 critical cases were enrolled for questionnaire interview, chest CT and exercise test (6MWT). For

lung function test, 70 sampled patients ascertained as eligible received complete PFTs. Twenty survivors refused to complete the lung diffusion function test. Moreover, sixty-seven survivors received a blood antibody test.

The demographic and characteristics of the study population are shown in Table S1. The mean age of these cases was 48.11 years and 40 (42.55%) of them were females. Only 7 of them were former smokers or current smokers. The most common comorbidity was hypertension (16 cases, 17.02%), followed by diabetes mellitus (9 cases, 9.57%), chronic heart disease (4 cases, 4.26%) and asthma (2 cases, 2.13%). Although 11 (11.70%) survivors were transferred to ICU, none of them required invasive mechanical ventilation. The overall duration of hospital stay was (15.08 ± 5.71) days. With regard to treatment, patients were mostly treated with antibacterial agents (82.98%), interferon (81.91%), corticosteroids (30.85%) and immunoglobulin (10.64%). All patients received antiviral treatment. The median duration from symptom onset to follow-up visit was 366.0 (355.0, 376.0) days, and the median time from the hospital discharge to follow-up visit was 345.0 (333.0, 349.0) days.

**Symptoms, HAMA, HAMD, mMRC and SF-36 questionnaires at 1-year follow up**

At 1-year follow up, 61.70% of patients (58 of 94) reported at least one symptom that did not exist before COVID-19 infection, including muscle fatigue (39.36%), insomnia (22.34%), joint paint (20.21%), headache (14.89%), hair loss (13.83%) and chest pain (13.83%) (Table 1). Eleven patients (11.70%) still experienced a smell or taste disorder. And the frequency of muscle fatigue in severe/critical COVID-19 is higher than that of mild/moderate COVID-19 ($P < 0.05$, Table 1). According to the results, the persistent symptoms, anxiety or depression and the mMRC dyspnoea scale

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of COVID-19 patients had no relation to age, which is consistent with the previous reports (Hui et al., 2005; Qin et al., 2021).

For anxiety symptoms, 30 (31.91%) patients were evaluated as mild/moderate anxiety and 9 (9.57%) patients were severe. For depression symptoms, 42.55% of patients presented altered depression scores, including mild/probable depression (31 cases, 32.98%), moderate/definite depression (6 cases, 6.38%) and severe depression (3 cases, 3.19%). Although there were only 25 patients who participated both in 3-month follow-up and 1-year follow-up, the HAMA and HAMD score of 25 enrolled survivors at 1-year follow-up was significantly lower than that of patients at 3-month follow-up (Figure 2). In addition, the prevalence of mMRC score ≥ 1 were 22 (23.40%). The SF-36 revealed that PF, RP, BP, VT, RE and MH reached the highest scores (95, 100, 74, 75, 100 and 76, respectively), while GH and SF reached the lowest scores (66 and 70, respectively).

**Lung function, 6MWT and chest CT at 1-year follow up**

The pulmonary function, 6MWT and chest CT results were shown in Table 2. Anomalies were noted in $FEV_1$% predicted in 16 of 90 cases (17.78%), $FEV_1$/FVC in 9 (10%), total lung capacity (TLC%) predicted in 4 cases (5.71%) and DLCO% predicted in 10 cases (14.29%). And there were 20% and 35.29% of mild/moderate COVID-19 patients developing impaired pulmonary diffusion capacities and abnormal chest imaging manifestations one year after discharge (Table 2). Lung function of 25 patients who participated in both 3-month follow-up(Zhao et al., 2020) and 1-year follow-up were collected. There was no significant difference in FVC%, FEV1% pred, FEV1/FVC and TLC% between patients at 3-month follow-up and 1-year follow-up. The diffusing capacity in COVID-19 patients 1-year after discharge

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was higher than that at 3-month follow-up, even though no significant difference between two groups (Table S3). All these results indicated that CT patterns of abnormalities may contribute to pulmonary interstitial damage. The median (IQR) distance in the exercise test was 504.00 (486.36, 540.00) meters with a median oxygen saturation of 97. There was no oxygen saturation below 90% (data not shown). We calculated the difference in the distance of the 6MWT between our cohort and the healthy population adjusted by sex, age, weight and height(Enright et al., 1998). The distance of the sampled participants showed a significant decrease compared to the healthy population (median:596.45, IQR: 514.50-635.19; $P < 0.0001$, Table S4).

Overall, a wide array of abnormalities in chest CT were detected in 67 survivors at 1-year follow-up, including 38 patients with local GGO (40.43%) and 2 patients with consolidation (2.13%). GGO, nodule and subpleural lines were the most frequent abnormalities in chest CT (40.43%, 29.79% and 14.89%, respectively). Fibrotic lesions were observed in 13.83% of these 94 patients. The median total CT score was 1.50 (IQR 0.00-3.25) and the median number of segments involved was 1.50 (IQR 0.00-3.00). According to Table 2, survivors with severe/critical cases showed a lower level of minimal oxygen saturation in 6MWT and a significantly higher CT score ($P < 0.05$). Furthermore, the follow-up CT in severe/critical patients showed a greater number of involved lobes (mild/moderate patients: 1.0 [0.0-2.0] vs. severe/critical patients: 2.0 [1.0-3.0]; $P < 0.05$). Chest imaging manifestations of 25 survivors who participated in both 3-month follow-up(Zhao et al., 2020) and 1-year follow-up were collected. Additionally, the patients at 3-month follow-up had higher total score of chest CT compared with that in late convalescence phase (Figure S1).

**Comparison of clinical characteristics between normal and abnormal chest CT**

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As shown in Table 3, the clinical characteristics of patients between normal and abnormal chest CT group were compared. Chest CT scan was performed for 94 patients and showed abnormalities in 67 survivors at 1-year follow-up. The median age for participants with abnormal CT was 52 (IQR 46-58), much older than that of the normal CT group (median: 40; IQR: 28-50). Furthermore, 79.10% patients of abnormal CT group had the symptom of cough, and this rate was remarkable higher than that of the normal CT group (55.56%). The median CXR peak score evaluated during the hospital stay was 6.00 (IQR, 3.00-12.00) for the abnormal CT group and 2.00 (IQR, 1.00-4.00).

There were plenty of differences in laboratory findings between normal and abnormal chest CT group. At hospital admission, patients had decreased lymphocyte count ($P$ = 0.014). For blood biochemistry, lower level of albumin ($P$ = 0.000) and higher level of LDH ($P$ = 0.012) in patients with abnormal chest CT were evidenced than those of normal CT group. The level of CRP was tremendously higher in abnormal CT group ($P$ = 0.003), indicating a more serious infection. With regard to treatment, participants in group abnormal CT were more likely to receive corticosteroids (37.31% vs 14.81%, $P$ = 0.009) than participants in normal CT group. After multivariable adjustment, participants with older age showed an OR 1.080 (95% CI: 1.013, 1.153) for abnormal CT at 1-year follow-up (Table 4).

**Lung function sequelae in COVID-19 patients 1-year after hospital discharge**

Ten in seventy survivors with COVID-19 had impaired DLCO% predicted at

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1-year follow-up. To figure out the differences between normal and impaired DLCO survivors, we compared demographics, clinical characteristics and laboratory parameters between two groups in Table 5. We found that laboratory parameters including red blood cell count, hemoglobin concentration, ALT and TP on admission were lower in impaired DLCO group, and the difference between two cohorts was statistically significant. Level of urea nitrogen in DLCO impaired group was higher in the DLCO normal group. Other variables between the impaired DLCO group and normal DLCO group showed no significant difference. Finally, we put age, sex and the history of smoking into the multivariable logistic regression model. We found that the higher level of urea nitrogen at admission were associated with DLCO% predicted < 80% (OR 1.004, 95%CI 1.001-1.006, $P$ = 0.021, Table 6).

**Dynamic changes of antibodies**

There were 55 and 67 survivors tested for SARS-CoV-2 IgG, IgM antibodies and NAbs against SARS-CoV-2 at 3-month and 1-year post discharge, respectively. The negative rate of SARS-CoV-2 IgG was 7.27% and 11.94% at 3-month and 1-year follow-up, respectively. And SARS-CoV-2 IgM turned negative in 60.00% (33 of 55 patients) 3-month after discharge. At 1-year follow-up after hospital discharge, the negative rate of IgM was 82.09% (55 of 67 patients). We observed the concentrations of SARS-CoV-2 IgG and IgM antibody in early convalescence phase was higher than those of survivors in late convalescence phase. Application of the manufacturer's advised cut-off of 30% resulted in 47 samples (85.45%) reporting as unambiguously

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positive for ‘neutralization’ at 3-month follow-up, whilst 55 of 67 participants (82.09%) who presented for follow-up displayed an efficient neutralization 1-year after hospital discharge. As shown in Figure 3, there was no difference in serum anti-S IgM level between the mild/moderate and severe/critical groups ($P > 0.05$) 1 year after discovery. The anti-N IgG level of participants was 29.73 (IQR: 14.92-39.56) for mild/moderate group and 46.76 (IQR: 24.59-63.78) for severe/critical group. A significant difference was observed between mild/moderate group and severe/critical group ($P < 0.05$). The neutralizing activity in sVNT was higher than that in the severe/critical group ($P < 0.05$). The same phenomenon is noticed in anti-N IgG and SARS-CoV-2 sVNT level during follow-ups of survivor patients, but not in anti-S IgM (Figure 3).

We also observed a significant correlation between the potent neutralizing activity in the SARS-CoV-2 sVNT and anti-N IgG antibodies. The neutralizing activity in sVNT was not significantly correlation with the level of anti-S IgM antibodies at 1-year follow up (Figure 4). It’s worth noting that patients produced robust NAb responses after SARS-CoV-2 infection, and the majority of antibody neutralizing activity persisted more than 1-year after infection.

**Discussion**

After the COVID-19 outbreak, plenty of studies have been performed to describe the sequalae of COVID-19 survivors after hospital discharge. Here, we performed the first study with 1-year follow-up duration performing the clinical consequences of

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adult patients recovering from SARS-CoV-2. We found that at 1-year after hospital discharge, a high proportion of survivors endorsed at least one symptom, particularly muscle fatigue, insomnia and joint paint. The most striking finding is the high proportion of patients with lung injury (71.28%) and DLCO impairment (14.29%) 1-year after discharge, although the severity of COVID-19 had no relation with abnormality of CT and DLCO. The levels of SARS-CoV-2 IgG, IgM, and the neutralizing activity were significantly lower than those in early convalescence phase.

All participants have been integrated in normal work. We found that muscle fatigue and sleep difficulties were most common even at 1-year after hospital discharge. The rates are lower than those reported in the 1-year follow-up study of SARS survivors(Tansey et al., 2007). A follow-up study of COVID-19 survivors showed that 29.5% of patients still had muscular fatigue at the 3-month follow-up(Gonzalez et al., 2021). A previous study reported that the most common 6-month consequences of COVID-19 in patients discharged from hospital were muscle fatigue (63%) and sleep difficulties (26%), whilst age was the risk factor for fatigue(Huang et al., 2021). However, age had no relationship with the symptoms in COVID-19 survivors in our study. Additionally, the results of questionnaires in this study showed that a considerable proportion of participants had the persistent psychological symptoms. This is consistent with data from previous COVID-19 survivors at one month follow-up after hospital treatment(Mazza et al., 2020). The distance of 6MWT were shorter than the reference values. The muscle fatigue and psychiatric consequences is likely to be caused by the immune response, virus infection, social isolation,

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potentially fatal illness and stigma.

A recent meta-analysis of CT imaging of COVID-19 patients showed 91.6% of patients showed abnormal pattern in chest imaging manifestations and patchy or GGO were the most common findings in the acute phase(Zhu et al., 2020). Two studies including some critical COVID-19 patients, showed that a prevalence of the chest CT abnormalities ranging from 80.7% to 53.91% at the 3- and 6-month follow-ups(Gonzalez et al., 2021; Huang et al., 2021). A recent study found that the rate of radiological anomalies in 39% and the median of CT score was 0.0 (IQR: 0.0-1.0) 7 months after recovery(Liu et al., 2021). The rate of radiographic anomalies and fibrosis was 71.28% and 8.51% in our cohort. Even with the high rate of lung injury on chest imaging, the median of CT score was 1.5 (IQR: 0.00, 3.25) at 1-year follow-up. The severe/critical COVID-19 patients showed significant increases in CT abnormalities compared with the mild/moderate patients at 1-year follow-up. Therefore, we can infer that chest CT imaging abnormalities caused by SARS-CoV-2 could gradually be resolved over time. Furthermore, factor associated with the lung damage on chest CT was age, which was consistent with the previous studies on SARS and MERS(Antonio et al., 2003; Chan et al., 2003; Chang et al., 2005; Feikin et al., 2015). And we could speculate that age might be predictor of radiological damage in patients recovered from COVID-19. Whether the remaining radiological anomalies completely resolve needs to be investigated in longer term and further large-scale studies.

A similar phenomenon could be noticeable with pulmonary function during

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follow-ups of survivor patients with COVID-19. At time of hospital discharge, findings from 110 patients with mild (n = 24), moderate (n = 67) and severe (n = 19) showed that DLCO anomalies were noted in 47.2% patients(Mo et al., 2020). The rate of impaired DLCO remained high 6 months after discharge (34.13%), although it was lower than that at the time of 3 months (54%)(Huang et al., 2021; Qin et al., 2021). A recent study showed that 82% of ICU patients with ARDS secondary to COVID-19 performed impaired DLCO at 3 months follow-up(Gonzalez et al., 2021). The result of lung function assessment in this study showed that 14.29% of participants had a lung carbon monoxide diffusion dysfunction 1 year after hospital discharge. This is consistent with data from pervious SARS 1 year follow-up studies(Hui et al., 2005; Ong et al., 2005). The severity of pulmonary inflammation in the acute phase might be the reason for fibroblast activation and impaired DLCO in the convalescence phase(Qin et al., 2021). We also found that the level of urea nitrogen was an independent factor of abnormal DLCO, which is agreement with previous studies(Izcovich et al., 2020; Mudatsir et al., 2020). Thus, our study helps clinicians and policy makers in tailoring management strategies for COVID-19 survivors to identify the impaired DLCO as early as possible, and to develop better centralized management and pulmonary rehabilitation.

Previous studies have shown that serum IgG and neutralizing antibodies against SARS-CoV and MERS-CoV can persist for an average of 2 years(Cao et al., 2007; Choe et al., 2017; Payne et al., 2016; Wu et al., 2007). Recent studies have shown that approximately 90% of the patient cohort remained SARS-CoV-2 IgG positive 3-6

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months following symptom onset(Maine et al., 2020; Rodda et al., 2021; Zhao et al., 2020). Regarding NAbs, 85% of patients had high NAbs titer 3-4 months post-symptom onset(Jiang et al., 2021). SARS-CoV-2 IgG titers and NAbs neutralizing activity at 1-year follow-up in recovered individuals in our cohort exhibited a significantly decrease compared with those at 3-month after hospital discharge. In our cohort, we found no difference in the seropositivity of the antibodies among survivors with COVID-19 between 3-month and 1-year after discharge. The decline of serum IgG and neutralizing antibodies observed in the present study indicates re-infection among recovered COVID-19 patients. Taken together, the findings from this study suggest that rising antibodies levels 1 year after hospital discharge in patients with COVID-19 and will have important implications, with regard to monitoring of the immune response against SARS-CoV-2 and establishing vaccination strategies.

There are several limitations to our study. Firstly, we have a small cohort with confirmed SARS-CoV-2 infection, whilst a larger sample size would be more ideal for this type of study. Secondly, the baseline data of PFTs and 6MWT are unavailable, so we could not know whether the observed abnormalities were already present prior to diagnosis with COVID-19. Thirdly, since only 2 patients with critical COVID-19 symptoms were enrolled, further efforts are needed to assess the long-term outcomes of critical COVID-19 survivors.

**Conclusions**

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In conclusion, a cohort of patients were mainly troubled with muscle fatigue or insomnia, anxiety or depression 1 year after hospital for COVID-19. Pulmonary structural abnormalities and functional impairment are common among those who were tested. The high level of urea nitrogen on hospitalization admission due to COVID-19 could effectively predict impaired DLCO after 1 year discharge. COVID-19 elicits immune response that persist and display functional hallmarks of antiviral immunity.

**Conflict of interest**

The authors declare no competing interests.

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**Ethical Approval and participation consent**

The study was approved by the First Affiliated Hospital of Zhengzhou University (2020-KY-61) and was registered with the Chinese Clinical Trial Registry, ChiCTR2000033186. The written informed consent was obtained from all the patients.

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**Figure Legends**

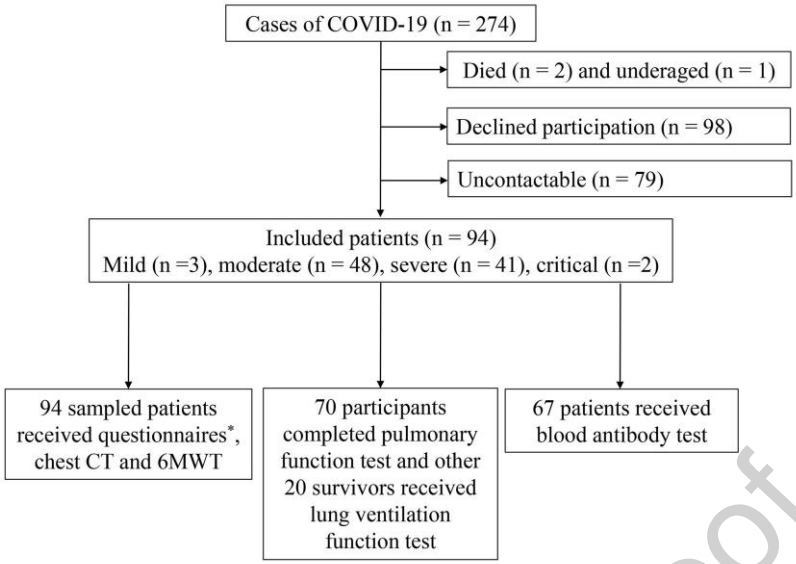


**Figure 1.** Flow chart of patients with COVID-19 at 1 year after hospital discharge between January 23 and February 27, 2020. * Questionnaires included general and respiratory symptoms, the 36-Item Short-Form Health Survey (SF-36), the 14-item Hamilton Anxiety Rating Scale (HAMA-14), the 24-item Hamilton Depression Rating Scale-24 (HAMD-24), and the modified British Medical Research Council (mMRC). 6MWT = 6-minute walking test.

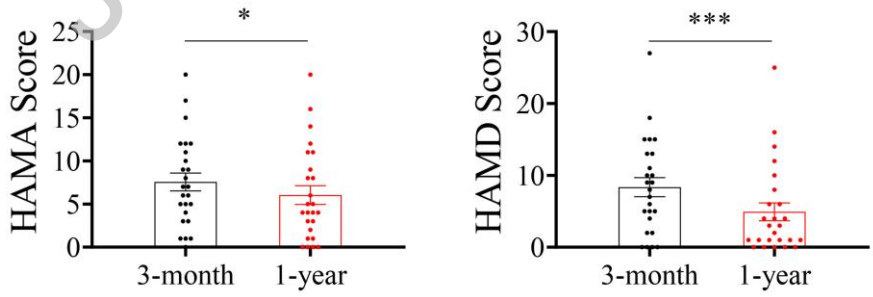


**Figure 2.** Comparison of the results of HAMA and HAMD scores between the 25 COVID-19 survivors at 3-month and 1-year follow-up. * $P < 0.05$; *** $P < 0.001$.

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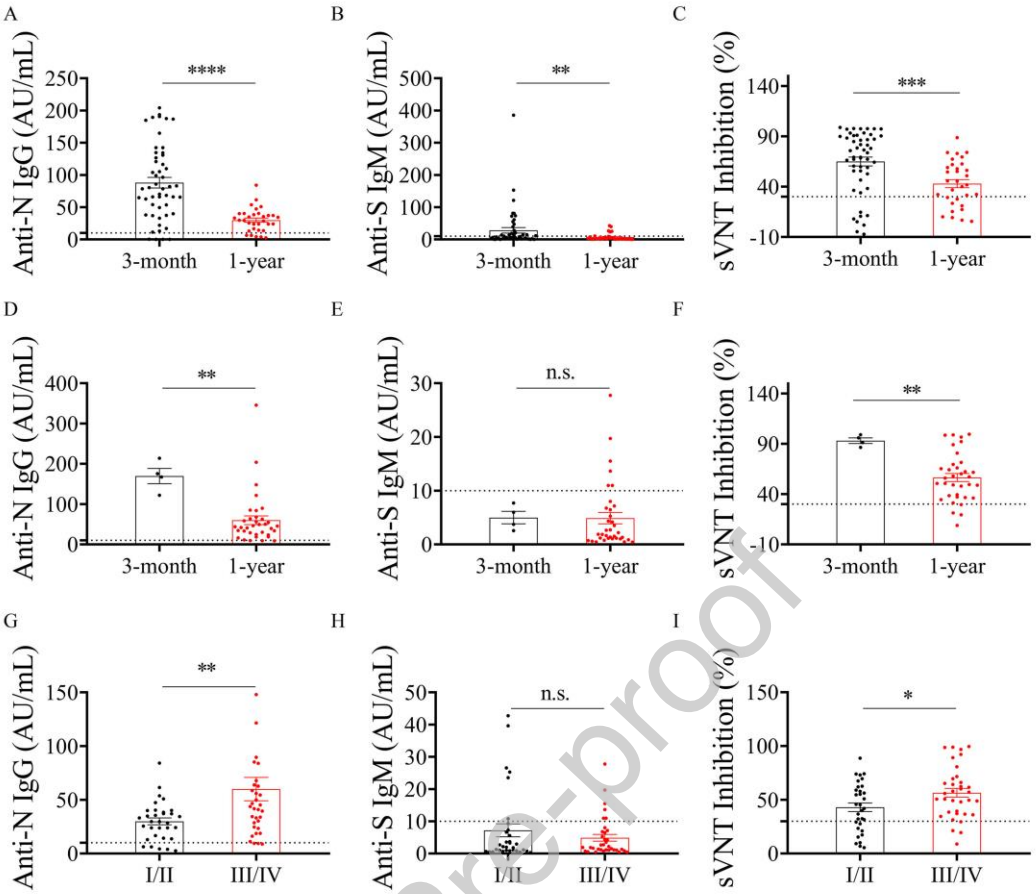


**Figure 3.** Anti-SARS-CoV-2 IgG and IgM antibody, neutralizing activity kinetics in the serum of patients with SARS-CoV-2 infection. The serum of 55 participants who participated in 3-month follow-up were collected, including 4 mild cases, 47 moderate cases and 4 severe cases. Of 67 survivors 1-year after discovery, 2.99% (2 cases) were classified as mild, 44.78% (30 cases) moderate, 49.25% (33 cases) severe and 2.99% (2 cases) critical. Comparison of anti-N IgG, anti-S IgM antibody concentration or neutralizing activity of patient serum in different COVID-19 groups in recovering status (Mild/moderate: A, B, and C; Severe/critical: D, E, and F). Distribution of anti-N IgG (D), anti-S IgM (E) antibody and sVNT inhibition (F) in different COVID-19 groups 1 year post charge (I/II = mild/moderate group; III/IV = severe/critical group). n.s., not significant; $^{*}P < 0.05$; $^{**}P < 0.01$; *** $P < 0.001$; $^{****}$

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$P < 0.0001$.

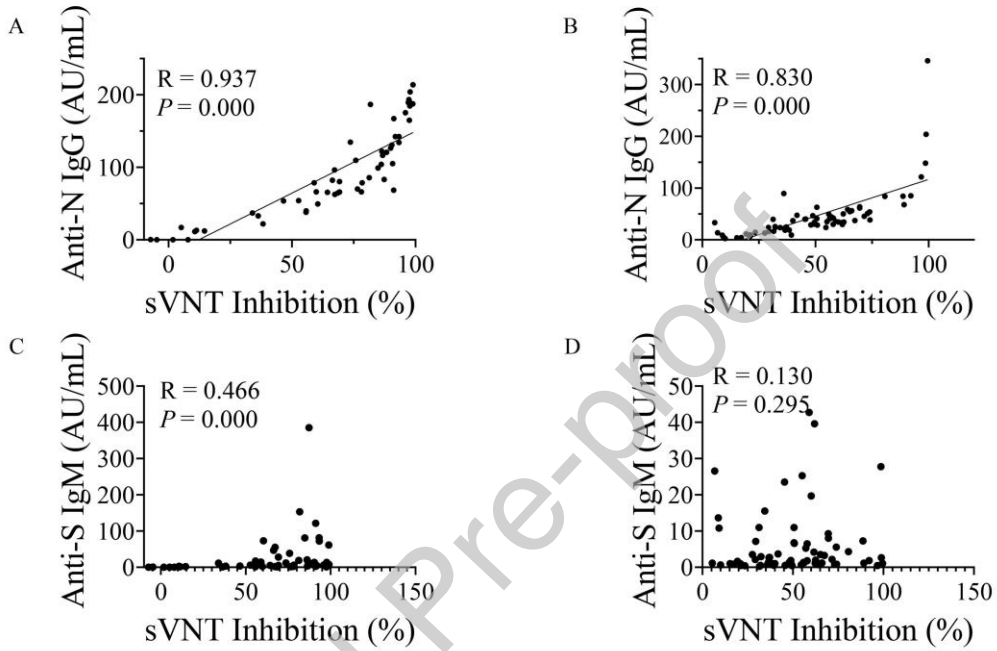


**Figure 4.** Neutralizing activity in sVNT correlates with anti-N IgG antibody. (A & B) Serum from 55 individuals was tested for antibodies against SARS-CoV-2 N IgG and neutralizing activity response at 3-month (A) and 1-year (B) after hospital discharge. (C & D) Serum from 55 or 67 individuals was tested for antibodies against SARS-CoV-2 S protein (IgM) and sVNT against neutralizing antibodies against SARS-CoV-2 that block the interaction with ACE2 cell surface receptor at 3-month (C) and 1-year (D) after discharge.

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**Table 1.** Symptoms and quality of life and anxiety/depression questionnaires results at 1-year follow-up

| Symptoms | | | | |
|---|---|---|---|---|
| | Total | Mild/moderate N = 51 | Severe/critical N = 43 | *P* |
| **Any one of the following symptoms,** N (%) | | | | |
| Muscle fatigue | 37 (39.36) | 15 (29.41) | 22 (51.16) | **0.032** |
| Insomnia | 21 (22.34) | 10 (19.61) | 11 (25.58) | 0.488 |
| Joint paint | 19 (20.21) | 7 (13.73) | 12 (27.91) | 0.088 |
| Headache | 14 (14.89) | 9 (17.65) | 5 (11.63) | 0.414 |
| Hair loss | 13 (13.83) | 5 (9.80) | 8 (18.60) | 0.218 |
| Chest pain | 13 (13.83) | 5 (9.80) | 8 (18.60) | 0.218 |
| Palpitations | 11 (11.70) | 6 (11.76) | 5 (11.63) | 0.984 |
| Smell or taste disorder | 11 (11.70) | 6 (11.76) | 5 (11.63) | 0.984 |
| Myalgia | 11 (11.70) | 7 (13.73) | 4 (9.30) | 0.506 |
| Dizziness | 10 (10.64) | 4 (7.84) | 6 (13.95) | 0.534 |
| Sore throat or difficult to swallow | 9 (9.57) | 5 (9.80) | 4 (9.30) | 1.000 |
| Diarrhea or nausea | 9 (9.57) | 6 (11.76) | 3 (6.98) | 0.664 |
| Skin rash | 2 (2.13) | 2 (3.92) | 0 | 0.498 |
| Questionnaires | | Mild/moderate | Severe/critical | *P* |

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| | | N = 51 | N = 43 | |
|---|---|---|---|---|
| **HAMA** | | | | 0.370 |
| No anxiety (≤ 6), N (%) | 55 (58.51) | 30 (58.82) | 25 (58.14) | |
| Mild/moderate anxiety (7-13), N (%) | 30 (31.91) | 18 (35.29) | 12 (27.91) | |
| Severe anxiety (≥ 14) | 9 (9.57) | 3 (5.88) | 6 (13.95) | |
| **HAMD** | | | | 0.646 |
| Normal (≤ 6), N (%) | 54 (57.45) | 32 (62.75) | 22 (51.16) | |
| Mild/probable depression (7-17), N (%) | 30 (31.91) | 15 (29.41) | 15 (34.88) | |
| Moderate/definite depression (18-24), N (%) | 7 (7.45) | 3 (5.88) | 4 (9.30) | |
| Severe depression (≥ 25), N (%) | 3 (3.19) | 1 (1.96) | 2 (4.65) | |
| **mMRC score** | | | | 0.344 |
| 0, N (%) | 72 (76.60) | 41 (80.39) | 31 (72.09) | |
| ≥ 1, N (%) | 22 (23.40) | 10 (19.61) | 12 (27.91) | |
| **SF-36** | | | | |
| Physical function (PF) | 95 (90, 100) | 95 (90, 100) | 95 (85, 100) | 0.150 |
| Role-physical (RP) | 100 (75, 100) | 100 (75, 100) | 100 (25, 100) | **0.037** |
| Body pain (BP) | 74 (61.75, 100) | 74 (52, 100) | 74 (64, 100) | 0.418 |
| General health perceptions | 66 (47, 80) | 65.49 ± 20.55 | 58.88 ± 25.81 | 0.179 |

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| (GH) | | | | |
| Vitality (VT) | 75 (63.75, 90) | 80 (65, 90) | 70 (60, 85) | 0.108 |
| Social function (SF) | 70 (40, 80) | 70 (50, 80) | 60 (40, 80) | 0.740 |
| Role-emotional (RE) | 100 (66.67, 100) | 100 (66.67, 100) | 100 (66.67, 100) | 0.502 |
| Mental health (MH) | 76 (60, 92) | 76 (60, 92) | 76 (64, 92) | 0.846 |

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**Table 2.** Pulmonary function, 6MWT and chest CT scan findings in all patients at 1-year follow-up.

| Pulmonary function | | | | |
|---|---|---|---|---|
| | | Mild/moderate (n = 50) | Severe/critical (n = 40) | *P* |
| FVC%, (n = 90) Normal range≥ 80% | 101.17 ± 16.60 | 102.59 ± 14.71 | 99.38 ± 18.73 | 0.364 |
| $FEV_1$% pred, (n = 90) Normal range ≥ 80% | 100.85 (87.88, 108.68) | 101 (88.55, 107.92) | 99.7 (84.88, 110.18) | 0.881 |
| ≥ 80%, N (%) | 74 (82.22) | 42 (84) | 32 (80) | 0.622 |
| < 80%, N (%) | 16 (17.78) | 8 (16) | 8 (20) | |
| $FEV_1$/FVC, (n = 90) Normal range ≥ 70% | 79.74 (75.86, 84.23) | 79.37 (75.75, 85.19) | 79.94 (76.47, 83.22) | 0.951 |
| ≥ 70%, N (%) | 81 (90) | 46 (92) | 35 (87.5) | 0.724 |
| < 70%, N (%) | 9 (10) | 4 (8) | 5 (12.5) | |
| | | Mild/moderate (n = 35) | Severe/critical (n = 35) | *P* |
| TLC%, (n = 70) Normal range ≥ 80% | 98.86 ± 12.24 | 100.34 (94.9, 108) | 94.98 (87.1, 106.5) | 0.079 |
| ≥ 80%, N (%) | 66 (94.29) | 33 (94.29) | 33 (94.29) | 1.000 |
| 50-80%, N (%) | 4 (5.71) | 2 (5.71) | 2 (5.71) | |
| RV%, (n = 70) | 105.96 (93.78, | 114.2 (95.3, | 102.1 (89.6, | 0.113 |

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|---|---|---|---|---|
| Normal range ≥ 65% | 117.96) | 124.26) | 114.49) | |
| DLCO%, (n = 70)<br>Normal range ≥ 80% | 99.50 ± 18.82 | 99.54 ± 21.62 | 99.46 ± 15.84 | 0.856 |
| ≥ 80%, N (%) | 60 (85.71) | 28 (80) | 32 (91.43) | 0.172 |
| 60-80%, N (%) | 10 (14.29) | 7 (20) | 3 (8.57) | |
| 6MWT (n = 94) | | Mild/moderate (n = 51) | Severe/critical (n = 43) | *P* |
| Distance (m) | 504 (486.36, 540) | 504 (498, 546) | 500 (468, 528) | 0.248 |
| Minimal oxygen saturation (%) | 97 (95, 98) | 98 (96, 99) | 96 (94, 98) | **0.001** |
| Chest CT (n = 94) | | Mild/moderate (n = 51) | Severe/critical (n = 43) | *P* |
| Density | | | | |
| Ground-glass, N (%) | 38 (40.43) | 18 (35.29) | 20 (46.51) | 0.270 |
| Volume of GGO, $cm^3$ | 0.00 (0.00, 0.32) | 0.00 (0.00, 0.12) | 0.00 (0.00, 0.88) | **0.033** |
| Consolidation, N (%) | 2 (2.13) | 0 | 2 (4.65) | 0.207 |
| Internal structures | | | | |
| Interlobular septal | 10 (10.64) | 3 (5.88) | 7 (16.28) | 0.196 |

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| thickening, N (%) | | | | |
| Subpleural lines, N (%) | 14 (14.89) | 6 (11.76) | 8 (18.60) | 0.353 |
| Nodule, N (%) | 28 (29.79) | 14 (27.45) | 14 (32.56) | 0.590 |
| linear opacities, N (%) | 13 (13.83) | 9 (17.65) | 4 (9.30) | 0.243 |
| Lesions | | | | |
| Reticulation, N (%) | 4 (4.26) | 1 (1.96) | 3 (6.98) | 0.492 |
| Fibrotic, N (%) | 8 (8.51) | 2 (3.92) | 6 (13.95) | 0.172 |
| CT score | | | | |
| Score, mean (SD) | 1.50 (0.00, 3.25) | 1 (0, 2) | 2 (1, 6) | **0.002** |
| Number of lobes involved, median (IQR) | 1.50 (0.00, 3.00) | 1 (0, 2) | 2 (1, 3) | **0.005** |

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**Table 3.** Univariate analysis of predictors of abnormal CT score.

| Parameters | Normal range | Normal CT group (N = 27) | Abnormal CT group (N = 67) | *P* value |
|---|---|---|---|---|
| **Age** | **≥ 18** | **40 (28, 50)** | **52 (46, 58)** | **0.000** |
| Sex, female (%) | | 11 (40.74) | 29 (43.28) | 0.504 |
| Incubation period, d | | 5 (2, 8) | 5 (3, 8) | 0.241 |
| Hospital period, d | | 12 (10, 17) | 15 (12, 18) | 0.079 |
| Temperature, ℃ | | 38.12 ± 0.81 | 38.14 ± 0.68 | 0.891 |
| History of smoking | | 1 (3.7) | 6 (8.96) | 0.657 |
| Comorbidities | | | | |
| Hypertension | | 3 (11.11) | 13 (19.40) | 0.509 |
| Diabetes Mellitus | | 3 (11.11) | 6 (8.96) | 1.000 |
| Chronic heart disease | | 1 (3.70) | 3 (4.48) | 1.000 |
| Severe/critical | | 1 (3.70) | 10 (14.93) | 0.239 |
| Signs and symptoms at admission | | | | |
| Fever, No. (%) | | 22 (81.48) | 61 (91.04) | 0.342 |
| **Cough, No. (%)** | | **15 (55.56)** | **53 (79.10)** | **0.021** |
| Feeble, No. (%) | | 9 (33.33) | 20 (29.85) | 0.741 |

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|---|---|---|---|---|
| Chest tightness, No. (%) | | 4 (14.81) | 18 (26.87) | 0.212 |
| **CXR peak score** | | **2.00 (1.00, 4.00)** | **6.00 (3.00, 12.00)** | **0.007** |
| **Laboratory data** | | | | |
| **Blood Routine** | | | | |
| Leucocyte count (× $10^9$/L) | 4-10 | 5.48 (4.75, 6.36) | 4.97 (3.92, 6.04) | 0.180 |
| Neutrophil count (× $10^9$/L) | 2-7 | 3.74 (2.29, 4.78) | 3.28 (2.36, 4.69) | 0.649 |
| **Lymphocyte count (× $10^9$/L)** | 0.8-4.0 | **1.69 (1.09, 1.97)** | **1.18 (0.91, 1.56)** | **0.014** |
| NLR | | 2.08 (1.31, 4.16) | 2.73 (1.73, 3.92) | 0.169 |
| Monocyte count (× $10^9$/L) | 0.12-0.80 | **0.37 (0.31, 0.45)** | **0.30 (0.19, 0.41)** | **0.036** |
| **Eosinophil count (× $10^9$/L)** | 0.02-0.50 | **0.03 (0.01, 0.10)** | **0.01 (0.00, 0.04)** | **0.003** |
| Red blood cell count (× $10^9$/L) | 3.50-5.50 | 4.70 ± 0.45 | 4.56 ± 0.57 | 0.286 |
| Hemoglobin concentration (g/L) | 110-160 | 138.78 ± 16.94 | 135.02 ± 19.33 | 0.380 |

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| Platelet count ($\times 10^{12}$/L) | 100-300 | 171.22 ± 59.28 | 169.87 ± 63.05 | 0.924 |
| **Blood Biochemistry** | | | | |
| AST, U/L | 0-40 | 24.00 (17.00, 29.00) | 25.00 (19.60, 37.00) | 0.224 |
| ALT, U/L | 0-40 | 18.00 (16.00, 37.10) | 21.60 (13.10, 40.10) | 0.454 |
| **Albumin, g/L** | **35-55** | **42.94 ± 5.07** | **39.25 ± 3.87** | **0.000** |
| TP, g/L | 60-85 | 67.42 ± 4.45 | 65.23 ± 5.83 | 0.082 |
| GGT, U/L | 0-47 | 21.00 (15.50, 35.60) | 26.00 (16.00, 52.40) | 0.547 |
| ALP, U/L | 20-150 | 60.00 (55.00, 76.20) | 61.00 (47.90, 74.50) | 0.655 |
| TBA, μmol/L | 0-15 | 3.50 (2.30, 5.00) | 2.80 (2.00, 4.40) | 0.652 |
| Total bilirubin, μmol/L | 0-24 | 10.20 (7.70, 15.60) | 9.70 (7.40, 13.44) | 0.590 |
| Direct bilirubin, μmol/L | 0.00-9.50 | 2.50 (1.52, 4.90) | 2.92 (2.02, 4.50) | 0.264 |
| Indirect bilirubin, μmol/L | 0-17.1 | 7.80 (5.70, 11.20) | 6.70 (5.10, 9.90) | 0.185 |
| Urea nitrogen, | 1700-8300 | 3.86 (2.80, | 4.03 (3.33, 5.17) | 0.188 |

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| | | | | |
|---|---|---|---|---|
| μmol/L | | 4.92) | | |
| Creatinine, μmol/L | 20.00-106.00 | 63.00 (50.00, 75.80) | 69.00 (56.30, 76.00) | 0.245 |
| UA, μmol/L | 200-428 | 272.10 ± 69.78 | 239.62 ± 73.35 | 0.052 |
| Glucose, mmol/L | 3.89-6.11 | 5.45 (4.84, 6.27) | 5.81 (5.16, 7.23) | 0.131 |
| TG, mmol/L | 0.00-1.70 | 1.59 (1.00, 2.00) | 1.14 (0.85, 1.58) | 0.059 |
| **LDH, U/L** | **100-240** | **171.7 (141.2, 227.0)** | **217.2 (170.0, 268.4)** | **0.012** |
| **Infection associated** | | | | |
| **CRP, mg/L** | 5-10 | **5.00 (2.00, 21.62)** | **15.00 (8.00, 30.27)** | **0.003** |
| **Blood coagulation** | | | | |
| Prothrombin time, s | 11-15 | 13.20 (11.70, 14.40) | 13.10 (11.70, 14.70) | 0.584 |
| INR | 0.8-1.5 | 1.06 ± 0.19 | 1.10 ± 0.18 | 0.367 |
| APTT, s | 14-21 | 27.80 (22.00, 35.20) | 28.10 (22.10, 35.70) | 0.848 |
| Thrombin time, s | 22-38 | 14.80 (12.40, 18.20) | 16.50 (12.60, 18.20) | 0.598 |
| Fibrinogen, g/L | 2-4 | 3.68 ± 1.18 | 3.91 ± 1.07 | 0.352 |

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| | | | | |
|---|---|---|---|---|
| D-dimer, μg/L | 0-500 | 290.00 (130, 390) | 290.00 (120, 410) | 0.987 |
| **Treatment** | | | | |
| **Corticosteroid, No. (%)** | | **4 (14.81)** | **25 (37.31)** | **0.009** |
| Interferon beta, No. (%) | | 22 (81.48) | 55 (82.09) | 1.000 |
| Immunoglobulin, No. (%) | | 1 (3.7) | 9 (13.43) | 0.166 |

Data are expressed as mean± SD, median (IQR) and No. (%). Comparisons were determined by Student's test, Mann-Whitney U test or $\chi^2$ test as appropriate.

**Abbreviations:** NLR, Neutrophil-lymphocyte ratio. ALT, Alanine aminotransferase. AST, Aspartate aminotransferase. TP, Total protein. GGT, Gamma-Glutamyl Transferase. ALP, Alkaline phosphatase. TBA, Total bile acids. GLO, Globulin. UA, Uric acid. TG, Triglyceride. CRP, C-reactive protein. LDH, lactate dehydrogenase. INR, international normalized ratio. APTT, Active partial thrombin time.

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**Table 4.** Multivariate analysis of predictors of abnormal CT score.

| | ***β*** | ***P* value** | **OR (95% CI)** | ***β*** [a] | ***P* value** [a] | **OR (95% CI)** [a] |
|---|---|---|---|---|---|---|
| Cough | -1.150 | 0.069 | 0.317 (0.092, 1.095) | -1.070 | 0.098 | 0.343 (0.097, 1.218) |
| **Age** | **0.072** | **0.024** | **1.075 (1.009, 1.144)** | **0.077** | **0.019** | **1.080 (1.013, 1.153)** |
| CXR peak score | 0.085 | 0.221 | 1.089 (0.950, 1.248) | 0.093 | 0.194 | 1.097 (0.954, 1.218) |
| Lymphocyte count | -0.060 | 0.604 | 0.942 (0.756, 1.173) | -0.061 | 0.606 | 0.941 (0.747, 1.185) |
| CRP | -0.009 | 0.557 | 0.991 (0.963, 1.021) | -0.008 | 0.588 | 0.992 (0.963, 1.022) |
| LDH | -0.001 | 0.840 | 0.999 (0.990, 1.008) | -0.002 | 0.741 | 0.998 (0.989, 1.008) |
| Albumin | -0.094 | 0.244 | 0.910 (0.776, 1.066) | -0.088 | 0.290 | 0.916 (0.779, 1.078) |
| Corticosteroid | -1.093 | 0.134 | 0.335 (0.080, 1.398) | -0.969 | 0.206 | 0.380 (0.085, 1.701) |

CI, confidence interval. a Logistic regression analysis for sex, the history of smoking and the symptom of chest tightness at admission.

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**Table 5.** Univariate analysis of predictors of abnormal DLCO% predicted.

| Parameters | Normal range | DLCO normal group (N = 60) | DLCO impaired group (N = 10) | *P* value |
|---|---|---|---|---|
| Age | ≥ 18 | 47.33 ± 12.29 | 48.90 ± 15.90 | 0.722 |
| Sex, female (%) | | 25 (41.67) | 6 (60) | 0.461 |
| Incubation period, d | | 5.00 (3.00, 7.00) | 4.00 (3.00, 6.00) | 0.494 |
| Hospital period, d | | 13.00 (10.00, 18.00) | 16.00 (11.75, 18.00) | 0.337 |
| Temperature, ℃ | | 38.20 (37.50, 38.68) | 38.00 (38.00, 38.35) | 0.880 |
| History of smoking | | 3 | 1 | 1.000 |
| Comorbidities | | | | |
| Hypertension | | 9 (15) | 3 (30) | 0.476 |
| Diabetes Mellitus | | 3 (5) | 1 (10) | 1.000 |
| Chronic heart | | 3 (5) | 1 (10) | 1.000 |

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| | | | | |
|---|---|---|---|---|
| disease | | | | 0 |
| Signs and symptoms at admission | | | | |
| Fever, N (%) | | 53 (83.33) | 9 (90) | 1.000 |
| Cough, N (%) | | 45 (75) | 8 (80) | 1.000 |
| Feeble, N (%) | | 19 (31.67) | 0 | 0.089 |
| Chest tightness, N (%) | | 15 (25) | 0 | 0.171 |
| CXR peak score | | 4.00 (1.00, 12.00) | 6.00 (3.00, 9.00) | 0.602 |
| CXR score | | 1.00 (0.00, 3.00) | 2.00 (0.00, 4.00) | 0.774 |
| **Laboratory data** | | | | |
| **Blood Routine** | | | | |
| Leucocyte count (× $10^9$/L) | 4-10 | 5.45 ± 1.85 | 4.74 ± 1.00 | 0.242 |
| Neutrophil | 2-7 | 3.73 ± 1.64 | 3.06 ± 1.13 | 0.21 |

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| | | | | |
|---|---|---|---|---|
| count (× $10^9$/L) | | | | 5 |
| Lymphocyte count (× $10^9$/L) | 0.8-4.0 | 1.23 (0.96, 1.71) | 1.13 (0.95, 1.64) | 0.724 |
| NLR | | 2.72 (1.99, 4.10) | 2.13 (1.61, 4.08) | 0.470 |
| Monocyte count (× $10^9$/L) | 0.12-0.80 | 0.33 (0.26, 0.44) | 0.34 (0.23, 0.46) | 0.968 |
| Eosinophil count (× $10^9$/L) | 0.02-0.50 | 0.01 (0.00, 0.04) | 0.02 (0.01, 0.05) | 0.378 |
| **Red blood cell count** (× $10^9$/L) | 3.50-5.50 | **4.72 ± 0.51** | **4.12 ± 0.46** | **0.001** |
| **Hemoglobin concentration (g/L)** | 110-160 | **139.16 ± 18.47** | **122.70 ± 14.58** | **0.009** |
| Platelet count (× $10^{12}$/L) | 100-300 | 160.00 (124.00, 195.50) | 155.00 (124.50, 199.25) | 0.987 |
| **Blood Biochemistry** | | | | |
| AST, U/L | 0-40 | 26.00 (17.08, 36.10) | 22.80 (19.10, 30.78) | 0.737 |
| **ALT, U/L** | **0-40** | **20.75 (15.13, 41.38)** | **16.50 (7.75, 22.40)** | **0.04** |

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| | | | | |
|---|---|---|---|---|
| | | | | **1** |
| Albumin, g/L | 35-55 | 41.06 ± 4.75 | 41.64 ± 2.87 | 0.711 |
| **TP, g/L** | 60-85 | **66.86 ± 5.19** | **63.25 ± 5.34** | **0.04** |
| | | | | **6** |
| GGT, U/L | 0-47 | 30.00 (16.55, 43.15) | 17.60 (13.00, 28.20) | 0.113 |
| TBA, μmol/L | 0-15 | 3.50 (2.30, 5.08) | 2.40 (1.98, 2.85) | 0.10 |
| | | | | 2 |
| Total bilirubin, μmol/L | 0-24 | 9.15 (7.11, 12.95) | 8.33 (6.15, 13.25) | 0.79 5 |
| Direct bilirubin, μmol/L | 0.00-9.50 | 2.85 (1.90, 4.58) | 2.30 (1.35, 2.99) | 0.12 9 |
| Indirect bilirubin, μmol/L | 0-17.1 | 6.26 (4.68, 8.38) | 5.57 (5.03, 10.03) | 0.69 9 |
| **Urea nitrogen, μmol/L** | 1700-8300 | **4024.33 ± 1183.33** | **5837.00 ± 1549.66** | **0.00 0** |
| Creatinine, μmol/L | 20.00-106.0 0 | 65.80 ± 11.60 | 68.73 ± 16.16 | 0.48 9 |
| UA, μmol/L | 200-428 | 252.82 ± 71.61 | 256.34 ± 75.65 | 0.88 |

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| | | | | |
|---|---|---|---|---|
| | | | | 7 |
| Glucose, mmol/L | 3.89-6.11 | 5.77 (5.07, 6.49) | 5.79 (5.33, 6.62) | 0.873 |
| TG, mmol/L | 0.00-1.70 | 1.12 (0.82, 1.61) | 1.36 (1.09, 1.71) | 0.343 |
| LDH, U/L | 100-240 | 195.80(149.60-261.53) | 217.30(141.00-260.75) | 0.887 |
| **Infection associated** | | | | |
| CRP, mg/L | 5-10 | 11.15 (5.10, 28.53) | 9.45 (2.88, 23.06) | 0.615 |
| **Blood coagulation** | | | | |
| Prothrombin time, s | 11-15 | 13.20 (11.18, 14.78) | 14.45 (11.48, 15.55) | 0.373 |
| INR | 0.8-1.5 | 1.09 ± 0.21 | 1.09 ± 0.20 | 0.991 |
| APTT, s | 14-21 | 25.10 (20.13, 28.88) | 28.55 (25.40, 35.63) | 0.055 |
| Thrombin time, s | 22-38 | 17.65 (15.35, 24.73) | 14.80 (14.18, 19.13) | 0.113 |
| Fibrinogen, | 2-4 | 3.92 ± 1.15 | 3.78 ± 1.41 | 0.73 |

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| | | | | |
|---|---|---|---|---|
| g/L | | | | 0 |
| D-dimer, μg/L | 0-500 | 225.00 (82.50, 400.00) | 280.00 (255.00, 360.00) | 0.306 |
| **Treatment** | | | | |
| Corticosteroid, No. (%) | | 20 (33.33) | 0 (0) | 0.075 |
| Interferon beta, No. (%) | | 57 (95) | 8 (80) | 0.297 |
| Immunoglobulin, No. (%) | | 3 (5) | 1 (10) | 1.000 |

Data are expressed as mean± SD, median (IQR) and No. (%). Comparisons were determined by Student's test, Mann-Whitney U test or $\chi^2$ test as appropriate.

**Abbreviations**: NLR, Neutrophil-lymphocyte ratio. ALT, Alanine aminotransferase. AST, Aspartate aminotransferase. TP, Total protein. GGT, Gamma-Glutamyl Transferase. ALP, Alkaline phosphatase. TBA, Total bile acids. GLO, Globulin. UA, Uric acid. TG, Triglyceride. CRP, C-reactive protein. LDH, lactate dehydrogenase. INR, international normalized ratio. APTT, Active partial thrombin time.

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**Table 6.** Multivariate analysis of predictors of abnormal DLCO.

| | ***β*** | ***P* value** | **OR (95% CI)** | ***β*** [a] | ***P* value** [a] | **OR (95% CI)** [a] |
|---|---|---|---|---|---|---|
| Red blood cell count | -4.253 | 0.169 | 0.014 (0.000, 6.063) | -4.884 | 0.127 | 0.008 (0.000, 4.037) |
| Hemoglobin concentration | -0.095 | 0.318 | 0.909 (0.754, 1.096) | 0.002 | 0.987 | 1.002 (0.784, 1.281) |
| ALT | -0.249 | 0.096 | 0.780 (0.582, 1.045) | -0.227 | 0.139 | 0.797 (0.590, 1.076) |
| TP | -0.121 | 0.523 | 0.886 (0.611, 1.285) | -0.304 | 0.189 | 0.738 (0.468, 1.162) |
| **Urea nitrogen** | **0.004** | **0.032** | **1.004 (1.000, 1.007)** | **0.003** | **0.021** | **1.004 (1.001, 1.006)** |

CI, confidence interval. TP, total protein. [a] Logistic regression analysis adjusted for age, sex and history of smoking.

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